

In the Specification:

Please amend the specification as shown:

Please delete the paragraph on page 6, lines 12-27, and replace it with the following paragraph:

Figure 3: is an alignment of the predicted protein sequences of GFR α family members. The sequence of rat GFR α -4 variants A and B (SEQ ID NOS: 8 and 9, respectively), rat GFR α -1 (**SEQ ID NO: 35**, EMBL acc. no. U59486), rat GFR α -2 (**SEQ ID NO: 34**, EMBL acc. no. AF003825), mouse GFR α -3 (**SEQ ID NO: 33**, EMBL acc. no. AB008833) and chicken GFR α -4 (**SEQ ID NO: 32**, EMBL acc. no. AF045162) were aligned using the ClustalW alignment program (EMBL, Heidelberg, Germany). Amino acid residues conserved between all 6 proteins are included in the black areas. Residues conserved between 4 or 5 of the sequences are shaded in grey. Cysteine residues conserved between all six GFR α 's are indicated with an asterisk above the sequence. Amino acid residues are numbered to the right. The dashes indicate gaps introduced into the sequence to optimize the alignment.

Please delete Table 4 on page 35, and replace it with the following Table:

Table 4: Intron-exon structure of rat GFR α -4.

Exon	Size (bp)	Intron size (bp)	Splice acceptor	Splice donor	Corresponding GFR α -1 exon size (bp)
1	>124	560	---	GAGgtaaggaggt (SEQ ID NO: 36)	---
2	355	49	ccctcaccagGGT (SEQ ID NO: 37)	CCGgtgcgtgcgg (SEQ ID NO: 38)	337
3	110	80	gcgcgcgcagGCC (SEQ ID NO: 39)	TAGgtacgctggg (SEQ ID NO: 40)	110
4	135	741	gtccctgcagGCA (SEQ ID NO: 41)	TGGgtgagggggc (SEQ ID NO: 42)	135
5	92	139 (varA) 84 (varB)	cactccatagATG (SEQ ID NO: 43)	CGGgtaggtatgg TGGgtgctgtttc (SEQ ID NOS 44 and 45)	182
6	>137	---	ttgtcccaagGTG cccttctcagGCA (SEQ ID NOS 46 and 47)	—	753

Please delete the paragraph on page 38, line 19, to page 40, line 38, and replace it with the following paragraph:

Specific binding of persephin to GFR α -4.

Constructs for the expression of soluble GFR α -IgG-Fc fusion proteins were made as follows. cDNA regions of human GFR α -1, GFR α -2 and GFR α -3, chicken GFR α -4 and rat GFR α -4 variant A (coding for amino acid residues 27 to 427, 20 to 431, 28 to 371, 20 to 399 and 29 to 252, respectively), excluding the sequences coding for the signal peptide and for the COOH-terminal hydrophobic region involved in GPI-anchoring, were cloned in-frame in the expression vector Signal plg plus (R&D Systems Europe Ltd, Abingdon, UK). The inserts of all constructs were confirmed by complete DNA sequence analysis. The resulting proteins expressed from these constructs contain a 17 amino acid residue NH₂-terminal CD33 signal peptide, the respective GFR α protein region and a 243 amino acid residue COOH-terminal human IgG₁-Fc fusion domain. Fusion proteins were expressed in CHO cells and purified as described. Chinese hamster ovary (CHO) cells were routinely cultured in DMEM/F12 medium supplemented with 10 % heat inactivated fetal calf serum. Cells were transfected with GFR α -IgGFc fusion constructs using an optimized Lipofectamine Plus method. For this, a total amount of 6.5 μ g DNA was incubated with 17.5 μ l PLUS reagent in 750 μ l serum free medium for 15 min at room temperature. Lipofectamine was diluted 50-fold into serum free culture medium, 750 μ l of this mixture was added to the DNA solution. Following a 15 min incubation at room temperature, 3.5 ml serum free medium was added, and the mixture was brought onto the cells (in a 100 mm petridish). The cells were incubated for 3h at 37°C in 5 % CO₂, after which 5 ml of culture medium, containing 20 % heat inactivated fetal calf serum, was added. 24 h later, the medium was changed into regular culture medium. Transfection efficiencies using these optimized conditions were typically 50-60%. For permanent transfections the selection medium contained either 800 μ g G418 or 800 μ g G418 and 800 μ g hygromycin. Antibiotic resistant clones were expanded and assayed for expression using specific antibodies. GFR α -IgGFc fusion proteins were purified from the medium of permanently or transiently transfected CHO cells by protein A chromatography. Bound protein was eluted with 0.1 M Na-citrate, pH 3.0 and collected into 1 M Tris buffer, pH 8.4 (dilution ratio 1:6). Protein concentration was estimated by absorbance at 280 nm using an extinction coefficient of 1.5. Surface plasmon resonance (SPR)

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experiments were performed at 25°C using a BIACORE 3000 instrument (Biacore AB, Uppsala, Sweden). Sensor chip CM5, the amine coupling kit and buffers used were also obtained from Biacore AB. Recombinant PSP, NTN, EVN/ART and GDNF were used as immobilised ligands. Recombinant human GDNF was obtained from R&D Systems Europe Ltd. (Abingdon, UK). NH₂-terminally 6His-tagged (**SEQ ID NO: 48**) recombinant human NTN, rat PSP and human EVN/ART were produced in *E. coli* as described previously (Creedon *et al.*, 1997). The carboxylated matrix of a CM5 sensor chip was first activated with a 1:1 mixture of 400 mM N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide and 100 mM N-hydroxy-succinimide for 10 min. Recombinant neurotrophic factors were applied onto the activated surface in 10 mM sodium acetate buffer, pH 4.5 at a flow rate of 5 µl/min. Unreacted carboxyl groups were blocked with 1 M ethanolamine-HCl. For binding experiments, soluble GFRα-IgGFc fusion proteins were superfused using the kinject program at 30 µl/min. Concentrations of GFRα-IgGFc used in kinetic experiments were between 1 and 100 nM in Hepes buffered saline (150 mM NaCl, 3.5 mM EDTA sodium salt, 0.005% polysorbate 20, 10 mM Hepes, pH 7.4). The association of the GFRα receptors to the immobilised ligands was monitored for 3 min and the dissociation for 1 min, followed by regeneration with 10 mM glycine buffer. Dissociation was initiated by superfusion with Hepes buffered saline. To improve the quality of sensor data, double referencing was used (Myszka, 1999). Data were analyzed using a global analysis with the BIACORE evaluation software (version 3.0.1). Global analysis calculates the association rate (k_a) and dissociation rate (k_d) simultaneously and the apparent equilibrium dissociation constant (K_D) is then calculated as k_d/k_a . A simple 1:1 Langmuir model was used to fit the data. Specific binding to PSP could be detected with both rat and chicken GFRα-4-IgGFc fusion proteins. The observed binding of GFRα-IgGFc was specific as there was no binding to GDNF, NTN or EVN/ART. Control experiments confirmed binding of GFR-1 to GDNF, of GFRα-2 to NTN and of GFRα-3 to EVN/ART. From the binding curves obtained using three determinations at differing concentrations of rat and chicken GFRα-IgGFc, the binding constants k_a (association rate) and k_d (dissociation rate) were derived (Table 6).